Notice of Allowability	Application No.	Applicant(s)
	09/994,143	CRAINE, BRIAN L.
	Examiner	Art Unit
	Yelena G. Gakh, Ph.D.	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Interview on 08/04/04*.

2. ☒ The allowed claim(s) is/are *1,5,9,11-22 and 30-45*.

3. ☒ The drawings filed on *26 November 2001* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☒ Interview Summary (PTO-413), Paper No./Mail Date *08/04/04* .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☐ Other _____.

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with Charles R. Hoffman on 08/03/04.

The application has been amended as follows:

Claims 25-29 are cancelled without prejudice.

Claims 2-4, 6-8, 10-12, 23-24 are cancelled.

The following claims are amended:

Claim 1 (currently amended). A method for determining whether blood in a stool came from an upper gastrointestinal site or a lower gastrointestinal site, comprising the steps of:

(a) collecting a stool sample containing hemoglobin and/or iron heme compounds derived from hemoglobin in its ferrous state and/or its ferric state and preparing ~~it~~ the stool sample at a predetermined pH for analysis by spectroscopy;

(b) ~~determining a sample absorption spectra of the stool sample~~ measuring an absorption spectrum of the stool sample at the predetermined pH using a spectrophotometer calibrated relative to a first absorption spectrum with a first Soret absorption peak approximately centered at a first wavelength of about 415 nanometers for pure ferrous heme at the predetermined pH and a second absorption spectrum with a second Soret absorption peak approximately centered at a second wavelength of about 408 nanometers for pure ferric heme at the predetermined pH; and

(c) determining whether the blood in the stool came from the upper gastrointestinal site or the lower gastrointestinal site based on an analysis of the stool sample absorption ~~spectra~~ spectrum by determining that the blood in the stool sample has passed through stomach acid and therefore came from the upper gastrointestinal tract if an absorption peak of a main Soret band of the stool sample absorption spectrum is closer to the second wavelength of about 408 nanometers than to the first wavelength of about 415 nanometers, or that the blood in the stool sample has

not passed through stomach acid and therefore came from the lower gastrointestinal tract if an absorption peak of the Soret band of the stool sample absorption spectra is closer to the first wavelength of about 415 nanometers than to the second wavelength of about 408 nanometers.

Claim 5 (currently amended). The method of claim 1 wherein step (a) includes ~~A method for determining whether blood in a stool came from an upper gastrointestinal site or a lower gastrointestinal site, comprising the steps of:~~

~~(a)~~ placing the stool sample into a sample tube containing a liquid buffer to create a sample stool suspension;

~~(b)~~ separating the sample stool suspension into a particulate matter portion and a liquid portion to create a fecal extract; and

~~(c)~~ filtering an amount of the fecal extract through a sample filter causing hemoglobin and related molecules present in the fecal extract to adhere to the sample filter~~;~~, and wherein step (d) includes measuring the sample absorption spectrum from hemoglobin and related molecules which adhere to the sample nitrocellulose filter.

~~(d) determining a sample absorption spectra of the sample filter relative to an absorption spectra of a reference filter that has not been exposed to the fecal extract using a spectrophotometer; and~~

~~(e) determining whether the blood in the stool came from the upper gastrointestinal site or for the lower gastrointestinal site based on a analysis of the sample absorption spectra.~~

Claim 9 (currently amended). The method of claim 5 wherein the filtering step includes ~~A method for determining whether blood in a stool sample came from an upper gastrointestinal site or a lower gastrointestinal site comprising the steps of:~~

~~(a) placing the stool sample into a sample tube containing a liquid buffer to create a sample stool suspension;~~

~~(b) separating the sample stool suspension into a particulate matter portion and a liquid portion to create a fecal extract;~~

~~(c)~~ filtering ~~an~~ the amount of the fecal extract through a sample nitrocellulose filter causing hemoglobin and related molecules present in the fecal extract to adhere to the sample nitrocellulose filter~~;~~

~~(d) determining a sample absorption spectra of the sample nitrocellulose filter relative to an identical reference nitrocellulose filter that has not been exposed to the fecal extract using a spectrophotometer; and~~

~~(e) classifying the type of gastrointestinal bleed based on a mathematical analysis of the sample absorption spectra~~.

Claim 13 (currently amended). The method of claim ~~9~~ 5 wherein the ~~sample~~ liquid buffer belongs to a group of aqueous hypotonic buffers that includes TE buffer comprised of 0.01M Tris[Hydroxymethyl]aminomethane, 0.001 M Ethylenediaminetetraacetic acid adjusted to pH 7.4.

Claim 14 (currently amended). The method of claim ~~9~~ 5 wherein the stool particulate matter is separated from the liquid phase by centrifugation and the resulting supernatant fraction becomes the fecal extract.

Claim 15 (currently amended). The method of claim ~~9~~ 5 wherein the stool particulate matter is separated from the liquid portion using a sample cassette, where the stool suspension is passed through a removable particulate barrier allowing the fecal extract to pass through the sample nitrocellulose filter and deposit the hemoglobin and related molecules onto the sample nitrocellulose filter.

Claim 17 (currently amended). The method of claim ~~9~~ 5 wherein ~~the~~ a mathematical analysis of the sample absorption spectra is accomplished by use of a trained artificial neural network running on a computing device.

Claim 18 (currently amended). The method of claim ~~9~~ 5 wherein ~~the~~ a mathematical analysis of the sample absorption spectra is performed by means of a Simplex method implemented on a

processor and using coefficients obtained from standard spectra for ferrohemoglobin, ferrihemoglobin, urobilinogen and fecal supernatant to maximize the function:

$$z = \varepsilon_{1,\lambda 420}x_1 + \varepsilon_{2,\lambda 420}x_2 + \varepsilon_{3,\lambda 420}x_3 + \varepsilon_{4,\lambda 420}x_4$$

where ε is the absorption coefficient for the indicated component (1-4) at the indicated wavelength (λ) obtained from the standard spectra, and x is the number of units of the indicated component (where component 1 is ferrohemes, component 2 is ferrihemes, component 3 is fecal supernatant, and component 4 is urobilinogen) and subject to the following constraining equations:

$$A_{\lambda 412}/\varepsilon_{2,\lambda 412} = \varepsilon_{1,\lambda 412}x_1 + \varepsilon_{2,\lambda 12}x_2$$

$$0 \geq x_4 - x_3$$

$$A_{\lambda 412} = \varepsilon_{1,\lambda 412}x_1 + \varepsilon_{2,\lambda 412}x_2 + \varepsilon_{3,\lambda 412}x_3 + \varepsilon_{4,\lambda 412}x_4$$

$$A_{\lambda 440} = \varepsilon_{1,\lambda 440}x_1 + \varepsilon_{2,\lambda 440}x_2 + \varepsilon_{3,\lambda 440}x_3 + \varepsilon_{4,\lambda 440}x_4$$

$$A_{\lambda 494} = \varepsilon_{1,\lambda 494}x_1 + \varepsilon_{2,\lambda 494}x_2 + \varepsilon_{3,\lambda 494}x_3 + \varepsilon_{4,\lambda 494}x_4$$

$$A_{\lambda 475} = \varepsilon_{1,\lambda 475}x_1 + \varepsilon_{2,\lambda 475}x_2 + \varepsilon_{3,\lambda 475}x_3 + \varepsilon_{4,\lambda 475}x_4$$

$$A_{\lambda 559} = \varepsilon_{1,\lambda 559}x_1 + \varepsilon_{2,\lambda 559}x_2 + \varepsilon_{3,\lambda 559}x_3 + \varepsilon_{4,\lambda 559}x_4$$

$$A_{\lambda 578} = \varepsilon_{1,\lambda 578}x_1 + \varepsilon_{2,\lambda 578}x_2 + \varepsilon_{3,\lambda 578}x_3 + \varepsilon_{4,\lambda 578}x_4,$$

where A is the absorption value at the indicated wavelength (λ) of the sample absorption spectra.

Claim 19 (currently amended). The method of claim ~~9~~ 5 wherein ~~the~~ a mathematical analysis of the sample absorption spectra is according to a Gaussian Jordan elimination algorithm, a singular value decomposition algorithm ~~of them~~, or an artificial neural network algorithm.

Claim 20 (currently amended). The method of claim ~~9~~ 1 wherein ~~the classification of the gastrointestinal bleed is determined~~ step (d) is performed by visual inspection of the sample absorption spectra.

Claim 21 (currently amended). The method of claim ~~9~~ 1 ~~wherein the method to purify the~~ including purifying hemoglobin and hemoglobin products in the stool sample ~~is~~ by means of one

of an affinity binding method, a phase separation method, a hydrophobic interaction method, and an antibody selection method.

Claim 22 (currently amended). The method of claim 9 1 wherein the sample absorption spectrum is obtained over the range of 400 to 600 nanometers.

Claim 30 (new). The method of claim 1 wherein the predetermined pH is equal to approximately 7.4.

Claim 31 (new). The method of claim 1 wherein the predetermined pH is an approximately neutral pH.

Claim 32 (new). A method for determining whether blood in a stool came from a lower gastrointestinal site, comprising the steps of:

(a) collecting a stool sample containing hemoglobin and/or iron heme compounds derived from hemoglobin in its ferrous state and/or its ferric state and preparing the stool sample at a predetermined pH for analysis by spectroscopy;

(b) measuring an absorption spectrum of the stool sample at the predetermined pH using a spectrophotometer calibrated relative to an absorption spectrum for pure ferrous heme at the predetermined pH having a Soret absorption peak approximately centered at a wavelength of about 415 nanometers, an α secondary absorption peak approximately centered at a wavelength of about 540 nanometers, and a β secondary absorption peak approximately centered at a wavelength of about 576 nanometers, and

(c) determining if the blood in the stool came from the lower gastrointestinal site based on an analysis of the stool sample absorption spectrum by determining that the blood in the stool sample has not passed through stomach acid and therefore came from the lower gastrointestinal tract if the stool sample absorption spectrum includes an α secondary absorption peak having a wavelength of about 540 nanometers and a β secondary absorption peak having a wavelength of about 576 nanometers.

Claim 33 (new). The method of claim 32 wherein the predetermined pH is equal to approximately 7.4.

Claim 34 (new). The method of claim 32 wherein the predetermined pH is an approximately neutral pH.

Claim 35 (new). A method for determining whether blood in a stool came from an upper gastrointestinal site or a lower gastrointestinal site, comprising the steps of:

(a) collecting a stool sample containing hemoglobin and/or iron heme compounds derived from hemoglobin in its ferrous state and/or its ferric state and preparing the stool sample at a predetermined pH for analysis by spectroscopy;

(b) measuring an absorption spectrum of the stool sample at the predetermined pH using a spectrophotometer calibrated relative to a first absorption spectrum with a first Soret absorption peak approximately centered at a first wavelength of about 415 nanometers for pure ferrous heme at the predetermined pH and a second absorption spectrum with a second Soret absorption peak approximately centered at a second wavelength of about 408 nanometers for pure ferric heme at the predetermined pH, the first absorption spectrum having an α secondary absorption peak approximately centered at a wavelength of about 540 nanometers and a β secondary absorption peak approximately centered at a wavelength of about 576 nanometers; and

(c) determining whether the blood in the stool came from the upper gastrointestinal site or the lower gastrointestinal site based on an analysis of the stool sample absorption spectrum by determining that the blood in the stool sample came from the lower gastrointestinal tract if an absorption peak of a main Soret band of the stool sample absorption spectrum is closer to the first wavelength of about 415 nanometers than to the second wavelength of about 408 nanometers and the stool sample absorption spectrum includes a first secondary absorption peak having a wavelength of about 540 nanometers and a second secondary absorption peak having a wavelength of about 576 nanometers, or by determining that the blood in the stool sample came from the upper gastrointestinal tract if an absorption peak of a main Soret band of the stool sample absorption spectrum is closer to the second wavelength of about 408 nanometers than to

the first wavelength of about 415 nanometers and the first and second secondary absorption peaks are not present.

Claim 36 (new). The method of claim 35 wherein the predetermined pH is equal to approximately 7.4.

Claim 37 (new). The method of claim 35 wherein the predetermined pH is an approximately neutral pH.

Claim 38 (new). A method for determining whether blood in a stool came from an upper gastrointestinal site or a lower gastrointestinal site, comprising the steps of:

(a) collecting a stool sample containing hemoglobin and/or iron heme compounds derived from hemoglobin in its ferrous state and/or its ferric state and preparing the stool sample at a predetermined pH for analysis by spectroscopy;

(b) measuring an absorption spectrum of the stool sample at the predetermined pH using a spectrophotometer calibrated relative to a first absorption spectrum for pure ferrous heme at the predetermined pH and a second absorption spectrum for pure ferric heme at the predetermined pH; and

(c) determining whether the blood in the stool came from the upper gastrointestinal site or the lower gastrointestinal site based on an analysis of the stool sample absorption spectrum by determining that the blood in the stool sample has passed through stomach acid and therefore came from the upper gastrointestinal tract if the stool sample absorption spectrum is closer to the second absorption spectrum than to the first absorption spectrum, or that the blood in the stool sample has not passed through stomach acid and therefore came from the lower gastrointestinal tract if the stool sample absorption spectra is closer to the first absorption spectrum than to the second absorption spectrum.

Claim 39 (new). The method of claim 38 wherein step (c) includes performing the analysis to determine if an absorption peak of a main Soret band of the first absorption spectrum is closer to approximately 408 nanometers than to 415 nanometers, and determining that the blood in the

stool sample came from the upper gastrointestinal tract if the main Soret band is closer to 408 nanometers.

Claim 40 (new). The method of claim 38 wherein step (c) includes performing the analysis to determine if α and β secondary absorption peaks of the stool sample absorption spectrum are present at approximately 540 nanometers and 576 nanometers, and determining that the blood in the stool sample came from the lower gastrointestinal tract if the absorption peaks are present.

Claim 41 (new). The method of claim 38 wherein step (c) includes classifying the type of gastrointestinal bleed based on a mathematical analysis of the stool sample absorption spectrum.

Claim 42 (new). The method of claim 41 including performing the mathematical analysis of the stool sample absorption spectrum by means of a trained artificial neural network running on a computing device.

Claim 43 (new). The method of claim 41 wherein the mathematical analysis of the sample absorption spectra is performed by means of a Simplex method implemented on a processor and using coefficients obtained from standard spectra for ferrohemoglobin, ferrihemoglobin, urobilinogen and fecal supernatant to maximize the function:

$$z = \varepsilon_{1,\lambda 420}x_1 + \varepsilon_{2,\lambda 420}x_2 + \varepsilon_{3,\lambda 420}x_3 + \varepsilon_{4,\lambda 420}x_4$$

where ε is the absorption coefficient for the indicated component (1-4) at the indicated wavelength (λ) obtained from the standard spectra, and x is the number of units of the indicated component (where component 1 is ferrohemes, component 2 is ferrihemes, component 3 is fecal supernatant, and component 4 is urobilinogen) and subject to the following constraining equations:

$$A_{\lambda 412}/\varepsilon_{2,\lambda 412} = \varepsilon_{1,\lambda 412}x_1 + \varepsilon_{2,\lambda 12}x_2$$

$$0 \geq x_4 - x_3$$

$$A_{\lambda 412} = \varepsilon_{1,\lambda 412}x_1 + \varepsilon_{2,\lambda 412}x_2 + \varepsilon_{3,\lambda 412}x_3 + \varepsilon_{4,\lambda 412}x_4$$

$$A_{\lambda 440} = \varepsilon_{1,\lambda\, 440}x_1 + \varepsilon_{2,\lambda\, 440}x_2 + \varepsilon_{3,\lambda\, 440}x_3 + \varepsilon_{4,\lambda\, 440}x_4$$

$$A_{\lambda 494} = \varepsilon_{1,\lambda\, 494}x_1 + \varepsilon_{2,\lambda\, 494}x_2 + \varepsilon_{3,\lambda\, 494}x_3 + \varepsilon_{4,\lambda\, 494}x_4$$

$$A_{\lambda 475} = \varepsilon_{1,\lambda 475}x_1 + \varepsilon_{2,\lambda 475}x_2 + \varepsilon_{3,\lambda 475}x_3 + \varepsilon_{4,\lambda 475}x_4$$

$$A_{\lambda 559} = \varepsilon_{1,\lambda 559}x_1 + \varepsilon_{2,\lambda 559}x_2 + \varepsilon_{3,\lambda 559}x_3 + \varepsilon_{4,\lambda 559}x_4$$

$$A_{\lambda 578} = \varepsilon_{1,\lambda 578}x_1 + \varepsilon_{2,\lambda 578}x_2 + \varepsilon_{3,\lambda 578}x_3 + \varepsilon_{4,\lambda 578}x_4,$$

where A is the absorption value at the indicated wavelength (λ) of the sample absorption spectra.

Claim 44 (new). The method of claim 38 including purifying hemoglobin and hemoglobin products in the stool sample by means of one of an affinity binding method, a phase separation method, a hydrophobic interaction method, and an antibody selection method.

Claim 45 (new). The method of claim 38 wherein the stool sample absorption spectrum is obtained over the range of 400 to 600 nanometers.

The following is an examiner's statement of reasons for allowance: the examiner's amendment approved by the Applicant withdraws the rejection under 35 U.S.C. 112, first paragraph; also, the prior art does not teach or fairly suggest the method steps recited in the amended claims.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yelena G. Gakh
8/4/04